

Amendments to the Claims

The listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Currently Amended) A method for determining the toxicity of a test compound by monitoring the effect of the test compound on cell differentiation of pluripotent stem cells, wherein the method comprises~~comprising~~:
 - (a) culturing undifferentiated pluripotent stem cells~~capable of differentiating into at least one particular cell type wherein said cells contain~~ having at least one recombinant nucleic acid molecule comprising a reporter gene encoding a product that is secreted upon cell differentiation and at least one cell type-specific promoter sequence operably linked to said reporter gene,~~or maintaining a non-human animal comprising said cells, under conditions allowing differentiation of said;~~ and
 - (b) contacting the undifferentiated pluripotent stem cells with the test compound;
 - (c) differentiating a portion of the pluripotent stem cells into at least one type of differentiated cells;
 - (d) determining the amount or activity of the reporter gene product within a body fluid of said transgenic non-human animal or the cell culture medium of said differentiated cells, wherein said reporter gene product comprises a secretory leader sequence, and wherein said secreted reporter gene product is not recaptured from said body fluid or cell culture medium;
 - (d) correlating the amount or activity of the secreted reporter gene product within the cell culture medium with a proportion of differentiated cells to undifferentiated pluripotent stem cells; and

- (e) determining the toxicity of the test compound by comparing the proportion of differentiated cells in the cell culture medium in the presence of the test compound with a control cell culture medium lacking the test compound, wherein a decreased proportion of differentiated cells in the presence of the test compound relative to the control is indicative of the test compound toxicity.
- 2-5. (Canceled)
6. (Previously Presented) The method of claim 1, wherein said at least one recombinant nucleic acid molecule further comprises an enhancer element.
7. (Currently Amended) The method of claim 1, wherein said differentiated cell type is selected from the group consisting of connecting fibroblasts, stromal cells, endothelial cells, glial cells, neural cells, neuronal cells, hematopoietic cells, smooth muscle cells, skeletal muscle cells, epithelial cells, and cardiac cells.
8. (Currently Amended) The method of claim 6, wherein ~~said promoter or~~ said enhancer is selected from the group consisting of α MHC, MLC2V, VE-cadherin, Tie-2, Flk-1, Fit-1, GFAP, alpha-1-tubulin and collagen 2 promoter or enhancer.
9. (Previously Presented) The method of claim 1, wherein said reporter gene product is secreted alkaline phosphatase (SEAP) or alpha-amylase.

10. (Withdrawn) The method of claim 1, wherein said recombinant nucleic acid molecule further comprises a selectable marker expressed by multi- or pluripotent cells.
11. (Currently Amended) The method of claim 1, wherein said pluripotent stem cells form cell aggregates or tissue-like aggregates derived from different cell types.
12. (Previously Presented) The method of claim 1, wherein said cells form embryoid bodies (EBs).
13. (Withdrawn) A reporter gene construct for monitoring cell differentiation comprising the recombinant nucleic acid molecule of claim 1.
14. (Withdrawn) A cell comprising a reporter gene construct of claim 13, wherein said cell is capable of differentiating into at least one particular cell type.
15. (Withdrawn) A cell aggregate of at least one cell type obtainable by the method of claim 1.
16. (Withdrawn) A tissue comprising said cell of claim 14.
17. (Withdrawn) An organ comprising said cell of claim 14.

18. (Withdrawn) An implant or transplant comprising an organ of claim 17, a tissue of claim 16, a cell of claim 14 or a cell aggregate of claim 15.
19. (Withdrawn) A non-human animal comprising a reporter gene construct of claim 13, a cell of claim 14, a cell aggregate of claim 15, a tissue of claim 16, or an organ of claim 17.
20. (Withdrawn) A composition of matter comprising a reporter gene of claim 13, a tissue of claim 16, cells of claim 14 or a cell aggregate of claim 15.
21. (Withdrawn) An array comprising a solid support wherein said cells of claim 14, said cell aggregate of claim 15 or said tissue of claim 16 are attached thereto.
22. (Withdrawn) An apparatus for analyzing the array of claim 21.
23. (Withdrawn) A method for obtaining, or profiling or both, a modulator of cell differentiation comprising:
 - (a) contacting a test sample comprising a cell of claim 14, with a test substance; and
 - (b) determining the effect of the test substance on the amount of the reporter gene product or activity compared to a control sample.

24. (Withdrawn) The method of claim 23, wherein said contacting further comprises contacting said test sample with at least one second test substance in the presence of said first test substance.
25. (Withdrawn) The method of claim 23, wherein a compound known to activate or inhibit the differentiation process is added to said test sample.
26. (Withdrawn) The method of claim 23, wherein the test substance is a therapeutic agent.
27. (Withdrawn) The method of claim 23, wherein the test substance is a mixture of therapeutic agents.
28. (Withdrawn) The method of claim 23, wherein preferably in a first screen said test substance is comprised in and subjected as a collection of test substances.
29. (Withdrawn) The method of claim 28, wherein said collection of test substances has a diversity of about 10^3 to about 10^5 .
30. (Withdrawn) The method of claim 29, wherein the diversity of said collection of test substances is successively reduced.
31. (Withdrawn) The method of claim 23, wherein said method is performed on an array.

32. (Withdrawn) The method of any one of claims 1 or 23, wherein said one or more cells are genetically engineered to over(express) or inhibit the expression of a target gene.
33. (Withdrawn) The method of claim 23, wherein said one or more cells or tissue are contained in a container.
34. (Withdrawn) The method of claim 33, further comprising taking three or more measurements, optionally at different positions within the container.
35. (Withdrawn) The method of claim 33, wherein said container is a well in a microtiter plate.
36. (Withdrawn) The method of claim 35, wherein said microtiter plate is a 24-, 96-, 384- or 1536-well plate.
37. (Withdrawn) A method of obtaining and manufacturing a drug which promotes or inhibits formation of specific cell types comprising the method of claim 23, wherein an enhanced or reduced level or activity of the reporter gene product is indicative for the drug.

38. (Withdrawn) A method of manufacturing an agent which supports wound healing or healing of damaged tissue or both comprising the method claim 23, wherein an enhanced level of activity of the reporter gene product is indicative for said agent.
39. (Withdrawn) A method of determining toxicity, preferably teratogenicity, embryotoxicity, chronic or acute toxicity of a test substance comprising the method of claim 23, wherein a reduced or enhanced level or activity of said reporter gene product is indicative for the toxicity of said test substance.
40. (Withdrawn) The method of claim 39, further comprising modifying said test substance to alter, eliminate or derivatize a portion of said test substance thereof that is suspected of causing toxicity, increasing bioavailability, solubility or half-life.
41. (Withdrawn) The method of claim 40, further comprising mixing the substance isolated or modified with a pharmaceutically acceptable carrier.
42. (Withdrawn) A kit useful for conducting a method of any one of claims 1 or 23, containing for example a reporter gene construct of claim 13, a cell of claim 14, and standard compounds, like cell culture media, selection agents, detection agents for the reporter molecule and control samples.
43. (Withdrawn) A method of conducting a drug discovery business comprising:

- (a) providing one or more assay systems of any of claims 1 or 23 for identifying a modulator of cell differentiation;
 - (b) conducting therapeutic profiling of modulators identified in step (a), or further analogs thereof, for efficacy and toxicity; and
 - (c) formulating a pharmaceutical preparation including one or more modulators identified in step (b) as having an acceptable therapeutic profile.
44. (Withdrawn) A method of conducting a target discovery business comprising:
- (a) providing one or more assay systems of any one of claims 1 or 23 for identifying modulators of cell differentiation;
 - (b) conducting therapeutic profiling of modulators identified in step (a) for efficacy and toxicity; and
 - (c) licensing, to a third party, the rights for further drug development or sales or both for modulators identified in step (a), or analogs thereof.
45. (Withdrawn) A modulator of cell differentiation such as growth and tissue formation promoting identified according to the method of claim 23.
46. (Withdrawn) A pharmaceutical composition for use in the modulation of cell differentiation comprising a modulator identified according to the method of claim 23.

47. (Withdrawn) A method for making a pharmaceutical composition for use in modulating cell differentiation comprising mixing a modulator of cell differentiation identified according to a method of claim 23 with a suitable diluents or carrier.
48. (Canceled)
49. (Withdrawn) A vector comprising the promoter region of the mouse alpha myosin heavy chain gene or of the ventricular myosin regulatory light chain gene, and operably linked thereto a heterologous DNA sequence.
50. (Withdrawn) The vector of claim 49, wherein said promoter comprises the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 2, or a fragment thereof.
51. (Withdrawn) The vector of claim 49, wherein said heterologous DNA sequence encodes a reporter or a selectable marker.
52. (Withdrawn) The vector of claim 51, wherein said DNA sequence encodes secreted alkaline phosphatase protein (SEAP).
53. (Withdrawn) The vector of claim 49, comprising the nucleotide sequence of SEQ ID NO: 3.
- 54-55. (Canceled)

56. (New) The method of claim 1, wherein said differentiated cell type is a cardiomyocyte.